BMC Endocrine Disorders

CASE REPORT

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Insulin-like growth factor-1 deficiency caused by hepatocellular adenoma leads to growth arrest, primary amenorrhea and metabolic syndrome: a case report and 4 years follow up

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Abstract

Background Hepatocellular adenoma (HCA) is a rare benign neoplasm, seldom ascribed as the cause of endocrine and metabolic derangement. We herein report a case of primary amenorrhea, growth arrest and metabolic syndrome. En bloc resection of the tumor normalized all the disturbances.

Case presentation A 16-year-old girl complained of primary amenorrhea and growth arrest for the past 2 years. Her height and weight were at the 3rd percentile, whereas waist circumference was at the 90th percentile for chronological age. She was hypertensive on admission. Plasma cholesterol, triglyceride and uric acid were elevated. Evaluation of GH/IGF-1 axis showed extremely low IGF-1 concentration, which was unresponsive to hGH stimulation. Computer tomography identified a huge liver mass (18.2 cm×13.7 cm×21 cm). The patient underwent an uneventful open right hepatic lobectomy. The tumor was en bloc resected. Immunohistochemistry indicated an unclassified HCA, which was confirmed by genetic screening. IGF-1 concentration, blood pressure, lipid profile and ovarian function were all normalized after surgery, and the girl had reduction in waist circumference and gain in height during the follow up.

Conclusion We provide evidence that liver-derived IGF-1 has a direct effect on skeletal and pubertal development, blood pressure, visceral adiposity and dyslipidemia independent of insulin resistance and obesity in the circumstance of undernutrition. Though rare, we propose the need to look into HCA cases for the existence of IGF-1 deficiency and its impact on metabolic derangement.

Keywords Hepatocellular adenoma, Insulin-like growth factor-1, Adiposity, Metabolic syndrome

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Background

Hepatocellular adenoma (HCA) is a rare benign liver neoplasm with reported prevalence between 0.001 and 0.004% [1]. It is most frequently diagnosed in women of reproductive age, the causes of which are usually associated with long-term use of oral contraceptive pills (OCPs) and obesity [2, 3]. Sporadic cases related to glycogen storage disease and maturity-onset diabetes of the young, type 3 (Mody3) as the causes of HCA in children and adolescents were also reported [4]. Molecular analysis categorizes HCA into 5 subtypes, including hepatocyte nuclear factor 1α (*HNF1A*) inactivated HCA, β-catenin (*CTNNB1*) mutated HCA, inflammatory HCA, sonic hedgehog HCA, and unclassified HCA [5]. Hepatocellular adenoma is usually asymptomatic, some are associated with malignancy transformation and hemorrhage, but seldom ascribed as the cause of endocrine and metabolic disturbance.

Herein, we report a case with growth arrest, primary amenorrhea and metabolic syndrome due to a huge HCA leading to insulin-like growth factor-1 (IGF-1) deficiency. En bloc resection of the tumor normalized IGF-1 concentration, ovarian function and metabolic derangement. To our knowledge, this is the first case of HCA associated with IGF-1 deficiency leading to endocrine and metabolic disturbance reported in the literature. Detailed information of changes in anthropometrics, metabolic and hormonal profiles before and after surgery with 4 years follow up are described.

Case presentation

The patient was a 16-year-old girl, complained of primary amenorrhea and no more height gain for the past 2 years. She was born at 31 gestational weeks as one of the quintuplets. Her birth weight was 1.25 kg and normal catch up was achieved. No chronic diseases or specific dietary habits were informed by the parents. The household financial condition was below average. The girl's height falling behind her siblings was only brought to attention in the recent 2 years. She did not complain of any abdominal pain. Her academic performance was above average in school. Familial history of hypertension and diabetes was denied.

Her height (150 cm) and weight (40 kg) were at the 3rd percentile, waist circumference (75 cm) was at the 90th percentile for chronological age. Tanner staging was I for the right breast and III for the left breast and for pubic hair. She was found to have elevated blood pressure (142/107mmHg), which was confirmed by ambulatory blood pressure monitoring averaged 148/101mmHg. Elevated total cholesterol (6.3mmol/L), triglyceride (2.66mmol/L) and uric acid (532μmol/L) were evident, while plasma glucose and serum insulin were normal (Supplementary Table 1). Free fatty acid (299μmol/L, normal range: 129–869μmol/L), indices for liver, kidney, thyroid and adrenal function were all within normal range. Bone age X-rays showed that the epiphyses of the proximal humerus, the distal ulna and radius, the ischial tuberosity, the proximal as well as the distal tibia and fibula were not fully closed, which indicated a mildly delayed bone age at 14.5 years.

The patient's growth hormone showed a moderate response upon administration of arginine and induction of hypoglycemia. IGF-1 and IGF-BP3 were extremely low for corresponding age, while IGF-1 was barely doubled in response to hGH stimulation. Ovarian function showed undetectable estradiol with suppressed LH, indicating hypogonadotropic hypogonadism. Both FSH and LH responded well to triptorelin stimulation (shown in Table 1).

Computer tomography identified a huge heterogeneous low-density and well demarcated liver mass, the size of 18.2 cm×13.7 cm×21 cm (shown in Fig. 1. a, b). Ultrasound-guided biopsy suggested HCA. The patient underwent an uneventful open right hepatic lobectomy and cholecystectomy. The tumor was en bloc resected and the capsule was intact. On the cut section, the tumor was macroscopically homogeneous with focal

Table 1 Stimulation tests for evaluation of GH/IGF-1 and gonadal axes before surgery

GH stimulation tests		**0**	**15′**	**30′**	**60′**	**90′**	**120′**
Insulin tolerance	Glucose (mmol/L)	4.6	1.2	4.8	-	5.2	5.6
(0.1U/kg, iv injection)	ACTH (pmol/L)	0.99	23.34	11.57	-	7.35	3.90
	GH (μg/L)	2.53	3.43	4.97	-	2.56	2.96
Arginine stimulation (0.5 g/kg, iv infusion)	GH (μg/L)	1.82	7.69	-	6.95	4.50	1.86
IGF-1 stimulation test (0.1U/kg hGH sc injection)	Baseline	Before injection		3rd day after		4th day after	5th day after
IGF-1(ng/mL) (normal: 226–903)	39.74	35.29		67.98		69.81	42.11
GnRH stimulation test		0		30′		60′	
Triptorelin stimulation	FSH (U/L)	7.3		13.08		13.76	
(0.1 mg sc injection)	LH (U/L)	2.6		15.26		14.83	

GH: growth hormone; IGF-1: insulin-like growth factor-1; IGF-BP3: insulin-like growth factor binding-protein-3; GnRH: gonadotropin-releasing hormone;

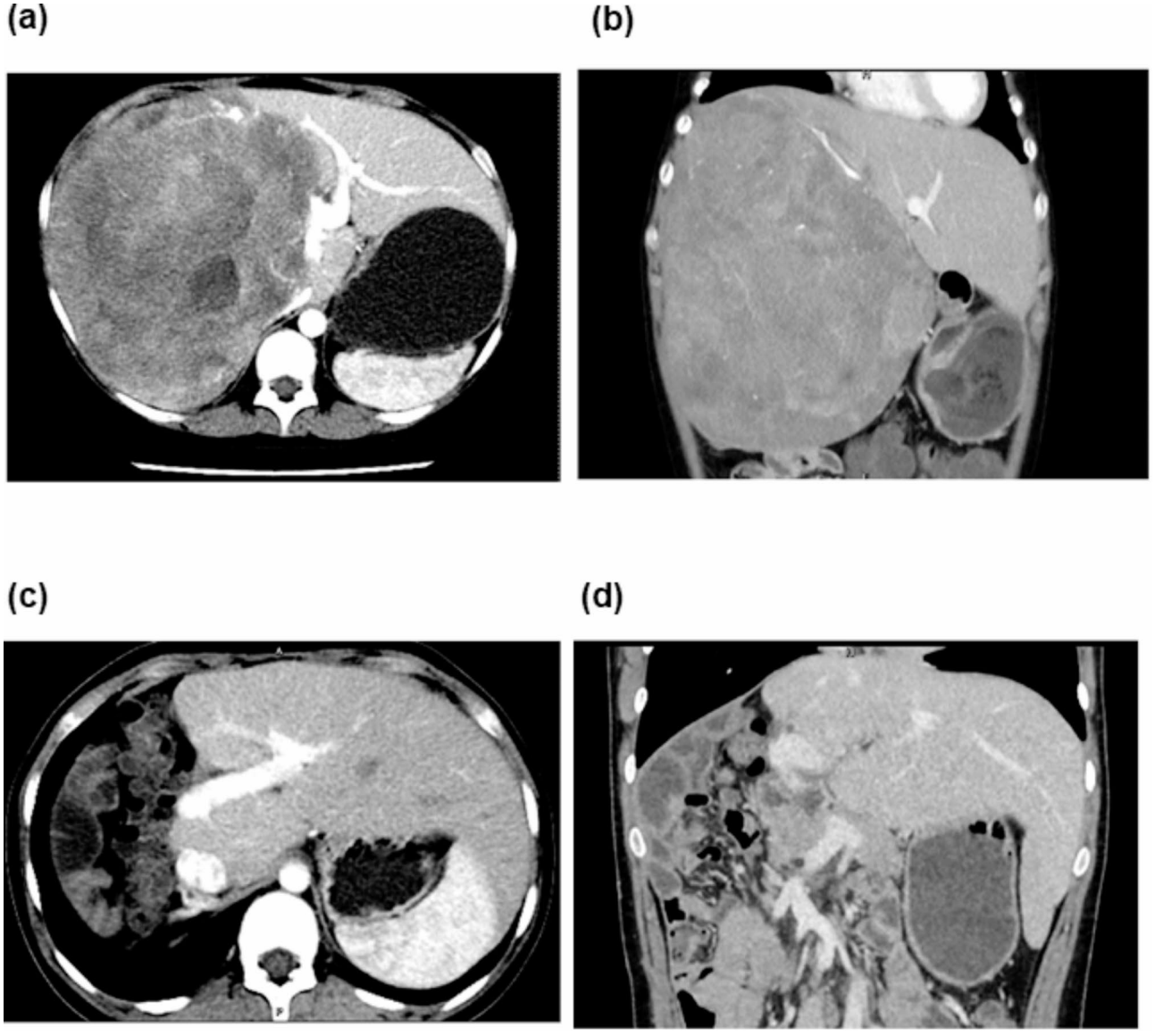

Fig. 1 CT scan on cross-section (**a**) and coronary section (**b**) of the abdomen before surgery, showing the right liver was completely occupied by a huge heterogeneous low-density mass with clear boundary. CT scan 1 year after surgery showed compensatory hypertrophy of the left and caudate lobes, no residue or recurrence was identified (**c**). Post-operational CT image on coronary section(**d**)

hemorrhage. Hematoxylin-eosin staining exhibited proliferous hepatocytes that arranged in cords or trabecula, where cytoplasmic vacuolar degeneration was conspicuous. Reticulin staining showed well-developed reticulate framework, and the plates were one or two cells' thick. Immunohistochemical staining was positive for liver fatty acid binding protein (LFABP), which excluded HNF-1a inactivated HCA, while negative for serum amyloid A (SAA), thus also ruling out inflammatory HCA. There was overexpression of GS on the tumor as compared to the surrounding normal liver tissue. However, β-catenin was only positive on the cellular membrane of the tumor, which was similar to normal hepatocytes, did not support the diagnosis of β-catenin mutated HCA. Thus, it was an unclassified HCA (shown in Fig. 2. a-h).

Whole exome sequencing on tumor samples identified 18 potentially deleterious single nucleotide variants, none of which was associated with the known HCA subtyping genes. Neither of these variants nor HCA related mutations were identified in the blood sample (Supplementary Table 2).

IGF-1 more than tripled just 3 days after surgery, achieved normal range 2 months later, and maintained within the upper quantile at 1 year and 2.5 years after surgery. Likewise, IGF-BP3 doubled its concentration 2 months after surgery and tripled at 1 year and maintained this level thereafter. In contrast, morning GH

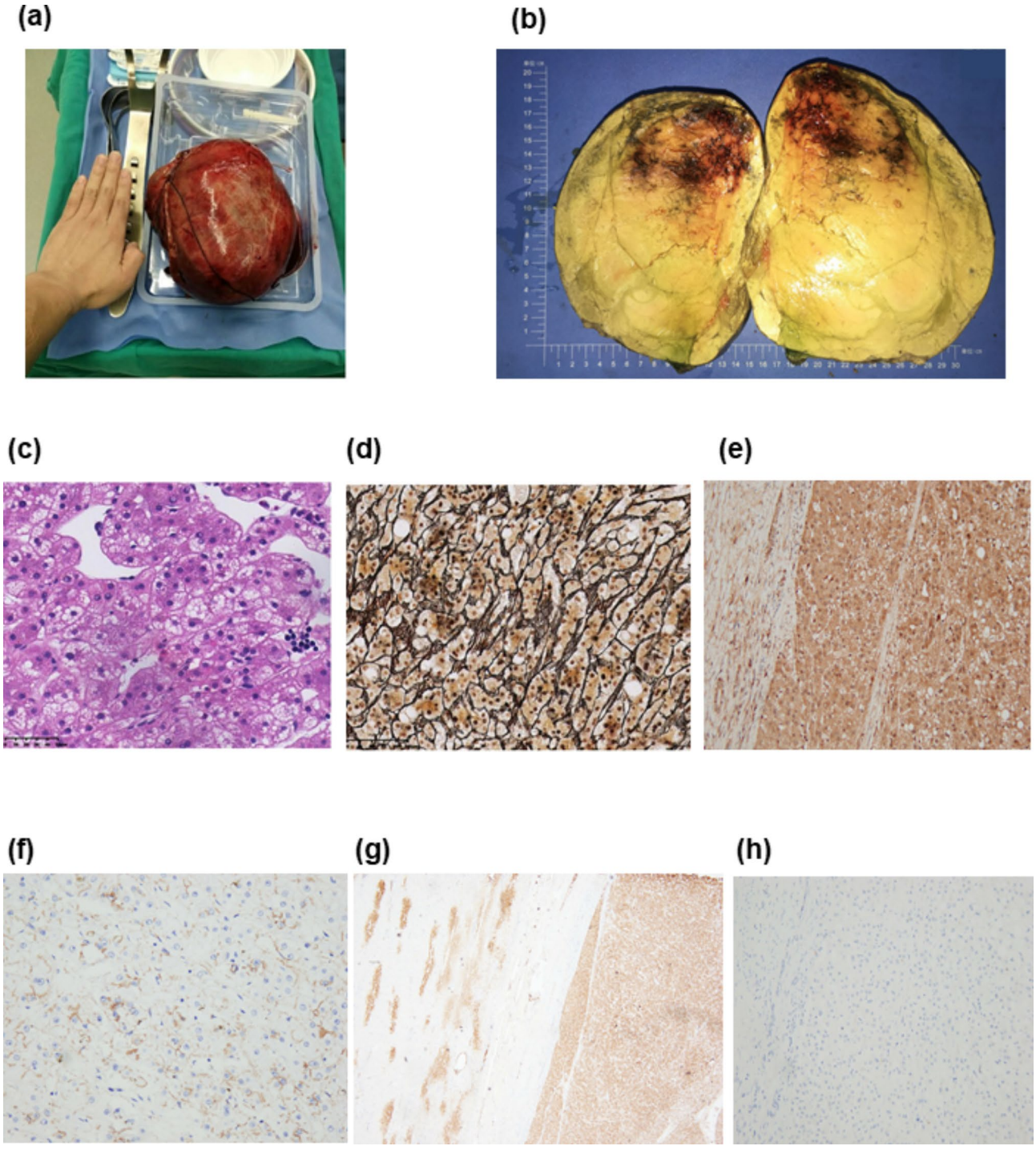

Fig. 2 The tumor was en bloc resected with a complete capsule, the size was 22 cm×21 cm×20 cm (**a**). On cut section, the tumor appeared yellow and macroscopically homogeneous with local hemorrhage (**b**). Hematoxylin-eosin staining exhibited proliferous hepatocytes arranged in cords or trabecula, where cytoplasmic vacuolar degeneration was conspicuous (400×) (**c**). Reticulin staining showed a well-developed reticulate framework (400×) (**d**). Presence of liver fatty acid binding protein (LFABP) expression (200×) excluded HNF-1a inactivated HCA(**e**). β-catenin staining was positive on the cellular membrane of the tumor and did not support the diagnosis of β-catenin mutated HCA (400×) (**f**). Overexpression of glutamine synthetase on the tumor (on the right) as compared to normal tissues on the left (100×) (**g**). The tumor stained negative for serum amyloid A (SAA), thus ruling out inflammatory HCA (200×) (**h**)

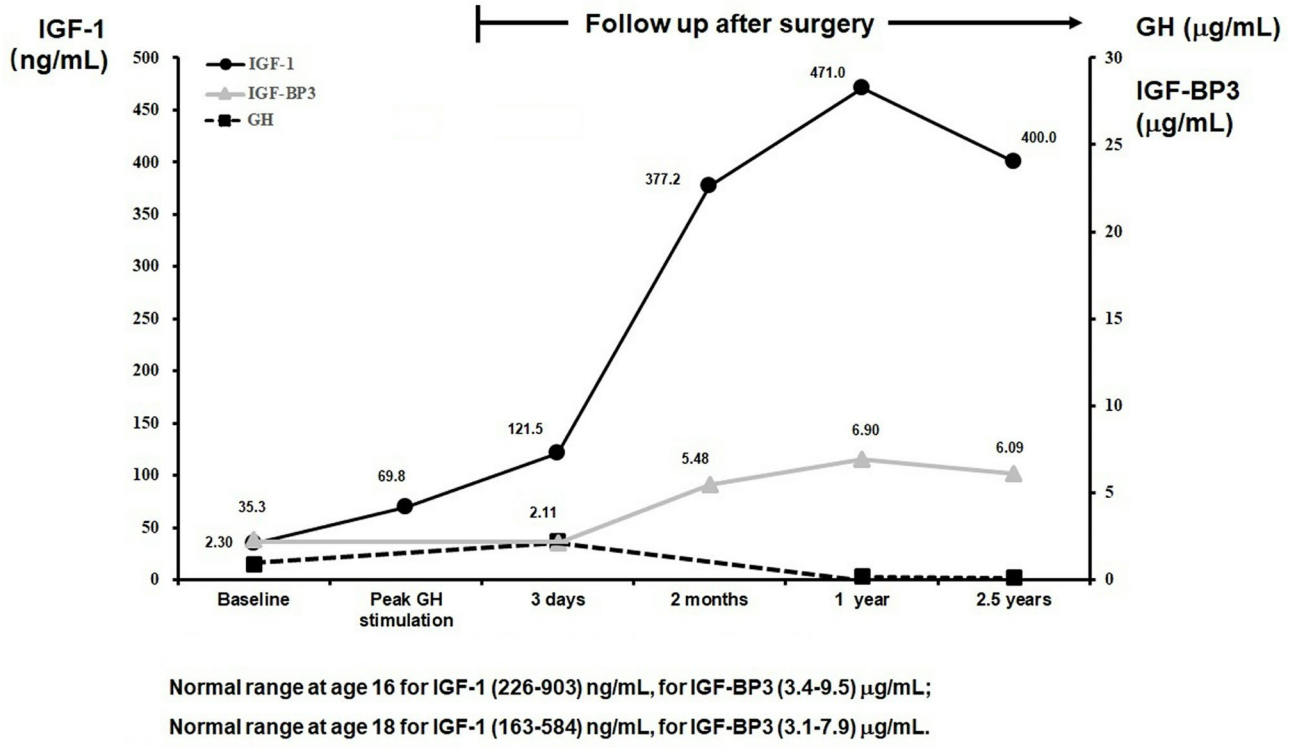

Fig. 3 IGF-1 concentration barely responded to hGH stimulation before surgery, while tripled on the 3rd day and achieved to normal range 2 months after surgery. IGF-BP3 tripled its concentration at 1 year after surgery as compared to baseline. In contrast, morning GH levels were suppressed after the surgery

levels were suppressed after the surgery as compared to baseline (shown in Fig. 3).

CT scan at 1 year showed the left and caudate liver lobes were compensatory hypertrophic. No residue or recurrent tumor was identified (shown in Fig. 1. c, d). X-ray of the left hand at 18.6 years showed that the distal and proximal metacarpophalangeal epiphysis and most of the distal ulna and radius epiphysis were closed.

The elevated total cholesterol, triglyceride, LDL-c and uric acid were all normalized while hypogonadotropic hypogonadism was corrected after surgery (Supplementary Table 1). The patient's menarche spontaneously started 6 months after surgery followed by regular cycles without hormone replacement.

The patient gained 2 cm in height and waist circumference was reduced by 5 cm 1 year after surgery. She grew another 2 cm in height and reduced another 7 cm in waist circumference at 2.5 years and maintained the figure at the 4 years' follow-up visit. In contrast, her siblings gained 1 to 4 cm in height but not much in weight in 4 years. None of them achieved target height calculated based on the height of the parents (Supplementary Table 3).

Discussion

GH/IGF-1 axis plays significant role in growth, initiation of puberty and metabolism. Circulating IGF-1 level is regulated by GH, while IGF-1 impacts GH secretion through a negative feedback mechanism. The relationship between GH and IGF-1 is complex, the effect of one cannot be considered mutually exclusive of the other [6]. Liver is the major site of IGF-1 production. Liver-derived IGF-1 comprises 75% of the serum concentration. In addition to the well-appreciated somatotropic effect on skeletal growth, recent evidence also showed a direct action of serum IGF-1 to stimulate a peptidergic pathway within the medial basal hypothalamus, leading to the removal of the prepubertal brake on GnRH secretion, allowing for the initial release of GnRH that triggers puberty onset [7]. We speculated that IGF-1 deficiency in our patient was due to the mass effect of the tumor that suppressed its release into circulation, or by reducing the effective hepatocellular mass that synthesized IGF-1, leading to growth arrest and primary amenorrhea. Before surgery, IGF-1 was unresponsive to hGH stimulation, whereas increased immediately after removal of the tumor, and normalized steadily with compensatory hyperplasia of the residual liver tissue. Baseline GH was mildly elevated as compared to those after surgery probably due to reduced negative feedback of IGF-1, and

somewhat responded to arginine and hypoglycemic stimulation. Nonetheless, GH alone was not potent enough to support the linear growth and pubertal initiation, indicating that the somatotropic potential of GH/IGF-1 on skeletal and pubertal development rely on the integral axis function, while IGF-1 might actually play a more dominant role.

The clinical features of the patient met with International Diabetes Federation criteria of metabolic syndrome for adolescents (BP≥130/85mmHg, waist circumference≥90th percentile, TG≥1.7mmol/L) [8], even though with an underdeveloped body figure, the condition of which was completely resolved after surgery, affirming the inherent relationship between IGF-1 deficiency and metabolic syndrome. Human and animal studies consistently showed that low IGF-1 was associated with hypertension, visceral adiposity and insulin resistance. IGF-1 participates in blood pressure regulation through activation of eNOS activity and nitric oxide production. Liver-specific IGF-1 knockout (LI-IGF-$1^{-/-}$) mice having a 79% reduction of serum IGF-1 exhibited increased blood pressure, which was associated with impaired vasorelaxation of the resistance vessels [9]. Previous studies had shown an inverse correlation between serum IGF-1 and visceral fat mass distribution [10]. However, the causality is less consistent, and usually considered bidirectional. Population studies also reported a conflicting relationship between circulating IGF-1 levels and insulin sensitivity ranging from none to U-shaped or positive associations [11–13]. It has been proposed that the elevated circulating FFA and adipokines induced by visceral adiposity is responsible for insulin resistance, thus markedly affecting the GH/IGF-1 axis via derangement of the classical feedback loop between GH and FFA released by GH-induced lipolysis. Conversely, the "functional" low GH/IGF-1 axis might induce unfavorable changes in body composition similar to that observed in GH-deficient patients, therefore contributing to the worsening of insulin resistance [6]. In contrast, Thankamony, et al. evaluated healthy adults with IGF-1 levels at the extreme quartiles of normal distribution during a 24-hour fast. The study showed reduced insulin secretion and increased hepatic insulin sensitivity in subjects with serum IGF-1 levels in the lowest quartile, who were with enhanced lipid metabolism, increased accumulation of intramuscular lipids and upregulation of genes for fat oxidation pathways in skeletal muscle [14]. The inconsistent results observed might be due to different study designs, heterogeneity of the subjects included with variable degrees and etiologies of IGF-1 deficiency, or different nutrition statuses. We did not make a detailed evaluation on insulin sensitivity in our patient. However, increased waist circumference in the circumstance of clinically underweight, without apparent hyperinsulinemia nor elevated FFA level, the condition of which probably resulted from undernutrition associated with the undesirable household financial situation, which also led to the underdevelopment of the siblings. Visceral adiposity and dyslipidemia were rectified soon after surgery. It might suggest a direct effect of liver-derived IGF-1 deficiency on visceral adipose accumulation and dyslipidemia without the accompanying insulin resistance in the circumstance of insufficient nutrient load.

Immunohistochemistry indicated unclassified HCA. Genetic screening further excluded other more common HCA subtypes adding up to over 90% of the whole entity. Whole exome sequencing identified 18 somatic deleterious variants, but we were unable to construct a signaling pathway model connecting these variants with HCA. Thus, the significance of these variants was unclear. In light of the causality of OCPs use and HCA occurrence, and with an improved formula, there has been a shift towards obesity as the contributing factor for the occurrence and development of HCA. Obesity and features of metabolic syndrome were frequently reported in HCA patients. Multiple and bilobar HCA were more common in obese patients [3]. IGF-1 deficiency has never been studied in patients with HCA. It happened to occur in a period of rapid linear growth and pubertal development, the delay of which aroused attention in our patient. In consideration of the close relationship between obesity and metabolic syndrome with IGF-1 deficiency, we propose that potential IGF-1 deficiency might have been overlooked in patients with large and multiple adenomas or adenomatosis as a contributing factor for obesity, especially visceral adiposity and metabolic syndrome, not the other way around.

In summary, we previously reported a case with growth arrest, primary amenorrhea and metabolic syndrome due to a huge HCA leading to IGF-1 deficiency at the Endocrine Society's annual meeting, ENDO 2020. We now present the 4 years follow-up of this case. We provide evidence that liver-derived IGF-1 has a direct effect on skeletal and pubertal development, blood pressure, visceral adiposity and dyslipidemia independent of insulin resistance and obesity in the circumstance of undernutrition. Though rare, we advocate the need to look into HCA cases for the existence of liver-derived IGF-1 deficiency and its impact on obesity and metabolic derangement.

Abbreviations

HCA	hepatocellular adenoma
Mody3	maturity-onset diabetes of the young, type 3
HNF1A	hepatocyte nuclear factor 1α
CTNNB1	β-catenin
IGF-1	insulin-like growth factor-1
GH	growth hormone
LFABP	liver fatty acid binding protein
GS	glutamine synthetase
SAA	serum amyloid A
FFPE	formalin-fixed paraffin-embedded

IGF-BP3	insulin-like growth factor binding-protein-3
LH	luteinizing hormone
FSH	follicle stimulating hormone
LI-IGF-1-/-	liver-specific IGF-1 knockout

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01716-z.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

We would like to thank the patient and her families who kindly consented to participate in the study. The initial investigation of the case was accepted as poster presentation at the Endocrine Society's annual meeting, ENDO 2020 and published as an abstract on *J Endocr Soc*.2020; 4 (Suppl_1): A10. https://doi.org/10.1210/jendso/bvaa046.019.

Author contributions

ZH collected data, wrote the original draft, reviewed and edited the manuscript, supported the study with funding. YWL managed and followed the patient and families, collected data and reviewed the manuscript. WC gave technical support in pathology, collected data and reviewed the manuscript. WD was involved in the follow up of the patient and families, collected data and reviewed the manuscript. YBL supervised the study, supported with funding, reviewed and revised the manuscript.

Funding

The study was funded by National Natural Science Fund of China (82070918; ZH), Key Field Research and Development Program of Guangdong Province, China (2019B020230001; YBL).

Data availability

The data generated during this study were included in this article and the supplementary materials. Further inquiries can be directed to the corresponding author: Zhimin Huang or Yanbing Li. Department of Endocrinology and Diabetes Center, The First Affiliated Hospital of Sun Yat-sen University, #58, Zhongshan Er Road, Guangzhou, Guangdong, P. R. China, 510080. E-mail: hzhim@mail.sysu.edu.cn (ZH). liyb@mail.sysu.edu.cn (YBL).

Declarations

Ethics approval and consent to participate

All procedures performed were in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University (Ethics review [2022] No.452). Written informed consent was obtained from the patient and family.

Consent for publication

Written informed consent with permission for publication without compromising privacy was obtained from the patient and her father. This work follows clinical case report guidelines (CARE).

Competing interests

The authors declare no competing interests.

Received: 30 July 2023 / Accepted: 3 September 2024
Published online: 12 September 2024

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